

Listing of the Claims:

This listing of claims will replace all prior versions and listing of claims in the application:

1-400. (Cancelled)

401.(Currently Amended) A method of expanding a population of hematopoietic stem cells *ex-vivo*, while at the same time, substantially inhibiting differentiation of the stem cells *ex-vivo*, the method comprising:

culturing said stem cells *ex-vivo* under conditions allowing for cell proliferation, said conditions comprising providing nutrients and cytokines and, at the same time, culturing said cells under conditions selected from the group consisting of:

~~conditions reducing expression and/or activity of CD38 in said stem cells;~~
~~conditions reducing capacity of said hematopoietic stem cells in responding to retinoic acid, retinoids and/or Vitamin D in said stem cells;~~
~~conditions reducing capacity of said stem cells in responding to signaling pathways involving the retinoic acid receptor, the retinoid X receptor and/or the Vitamin D receptor in said mononuclear cells; and~~

~~conditions wherein said stem cells are cultured in the presence of at least 0.1 mM of exogenously added nicotinamide, nicotinamide analog or nicotinamide derivative~~nicotinamide, a nicotinamide analog, a nicotinamide or a nicotinamide analog derivative or a nicotinamide or a nicotinamide analog metabolite;

thereby expanding the population of hematopoietic stem cells while at the same time, substantially inhibiting differentiation of saidthe stem cells *ex-vivo*.

402.(Withdrawn) A method of transplanting or implanting hematopoietic cells, said method comprising:

- (a) obtaining hematopoietic stem cells from a donor;
- (b) culturing said stem cells *ex-vivo* under conditions allowing for cell proliferation and, at the same time, culturing said cells under conditions selected from the group consisting of:
 - conditions reducing expression and/or activity of CD38 in said mononuclear cells,

APPLICANTS: Peled et al.

SERIAL NUMBER: 10/774,843

conditions reducing capacity of said hematopoietic mononuclear cells in responding to retinoic acid, retinoids and/or Vitamin D in said mononuclear cells,

conditions reducing capacity of said hematopoietic mononuclear cells in responding to signaling pathways involving the retinoic acid receptor, the retinoid X receptor and/or the Vitamin D receptor in said mononuclear cells; and

conditions wherein said mononuclear cells are cultured in the presence of nicotinamide, a nicotinamide analog, a nicotinamide or a nicotinamide analog derivative or a nicotinamide or a nicotinamide analog metabolite; and

(c) transplanting or implanting said stem cells to a recipient.

403. (Withdrawn) The method of claim 402, wherein said donor and said recipient are a single individual.

404. (Withdrawn) A method of genetically modifying stem cells with an exogene, said method comprising:

(a) obtaining stem cells to be genetically modified;

(b) culturing said stem cells ex-vivo under conditions allowing for cell proliferation

and, at the same time, culturing said cells under conditions selected from the group consisting of:

conditions reducing expression and/or activity of CD38 in said mononuclear cells,

conditions reducing capacity of said hematopoietic mononuclear cells in responding to retinoic acid, retinoids and/or Vitamin D in said mononuclear cells,

conditions reducing capacity of said hematopoietic mononuclear cells in responding to signaling pathways involving the retinoic acid receptor, the retinoid X receptor and/or the Vitamin D receptor in said mononuclear cells;

conditions wherein said mononuclear cells are cultured in the presence of nicotinamide, a nicotinamide analog, a nicotinamide or a nicotinamide analog derivative or a nicotinamide or a nicotinamide analog metabolite; and

(c) genetically modifying said stem cells with the exogene.

405. (Withdrawn) The method of claim 404, wherein the exogene is provided in a vector.

406. (Withdrawn) The method of claim 405, wherein the vector is a viral vector or a nucleic acid vector.

407. (Withdrawn) A method of adoptive immunotherapy comprising:

- (a) obtaining hematopoietic stem cells from a recipient;
- (b) culturing said stem cells ex-vivo under conditions allowing for cell proliferation and, at the same time, culturing said cells under conditions selected from the group consisting of:
 - conditions reducing expression and/or activity of CD38 in said stem cells,
 - conditions reducing capacity of said hematopoietic stem cells in responding to retinoic acid, retinoids and/or Vitamin D in said stem cells,
 - conditions reducing capacity of said hematopoietic stem cells in responding to signaling pathways involving the retinoic acid receptor, the retinoid X receptor and/or the Vitamin D receptor in said stem cells; and
 - conditions wherein said stem cells are cultured in the presence of nicotinamide, a nicotinamide analog, a nicotinamide or a nicotinamide analog derivative or a nicotinamide or a nicotinamide analog metabolite; and
- (c) transplanting said stem cells to the recipient.

408. (Withdrawn) A method of mobilizing bone marrow stem cells into the peripheral blood of a donor for harvesting the cells, the method comprising:

- (a) administering to the donor an effective amount of an agent selected from the group consisting of:
 - an agent that reduces expression and/or activity of CD38 in said cells,
 - an agent that reduces the capacity to respond to retinoic acid, retinoids and/or Vitamin D,
 - an agent that reduces the capacity to respond to signaling pathways involving the retinoic acid receptor, the retinoid X receptor and/or the Vitamin D receptor in said stem cells; and
 - an agent that is nicotinamide, a nicotinamide analog, a nicotinamide or a nicotinamide analog derivative or a nicotinamide or a nicotinamide analog metabolite; and
- (b) harvesting the cells.

409. (Withdrawn) The method of claim 408, further comprising administering to the donor at least one cytokine.

410. (Withdrawn) The method of claim 409, wherein said cytokine is selected from the group consisting of: stem cell factor, FLT3 ligand, interleukin-6, interleukin-1, interleukin-2, interleukin-10, interleukin-12, tumor necrosis factor- α , thrombopoietin, interleukin-3, granulocyte colony stimulating factor, macrophage colony stimulating factor, granulocyte/macrophage colony stimulating factor and erythropoietin.

411. (Currently Amended) A transplantable hematopoietic cell preparation comprising:
an expanded population of hematopoietic stem cells propagated *ex-vivo* in the presence of nutrients and cytokines and at least 0.1 mM of exogenously added ~~an effective amount of an agent that substantially inhibits differentiation of said stem cells, wherein said agent is selected from the group consisting of:~~
an agent that ~~reduces expression and/or activity of CD38 in said stem cells,~~
an agent that ~~reduces the capacity to respond to retinoic acid, retinoids and/or Vitamin D,~~
an agent that ~~reduces the capacity to respond to signaling pathways involving the retinoic acid receptor, the retinoid X receptor and/or the Vitamin D receptor in said stem cells; and~~
an agent that is nicotinamide, a nicotinamide analog or nicotinamide derivative, ~~a nicotinamide or a nicotinamide analog derivative or a nicotinamide or a nicotinamide analog metabolite;~~ and
a pharmaceutically acceptable carrier.

412. (Currently Amended) A method of expanding a population of hematopoietic stem cells *ex-vivo*, the method comprising:

obtaining adult or neonatal umbilical cord whole white blood cells or a whole bone marrow cells sample and

providing the cells in said sample with *ex-vivo* culture conditions for stem cells *ex-vivo* cell proliferation, said conditions comprising nutrients and cytokines and, at the same time, culturing said cells ~~under conditions selected from the group consisting of:~~

~~conditions reducing expression and/or activity of CD38 in said stem cells;~~

~~conditions reducing capacity of said hematopoietic stem cells in responding to retinoic acid, retinoids and/or Vitamin D in said stem cells;~~

~~conditions reducing capacity of said hematopoietic stem cells in responding to signaling pathways involving the retinoic acid receptor, the retinoid X receptor and/or the Vitamin D receptor in said stem cells; and~~

~~conditions wherein said stem cells are cultured in the presence of at least 0.1 mM of exogenously added nicotinamide, nicotinamide analog or nicotinamide derivative nicotinamide, a nicotinamide analog, a nicotinamide or a nicotinamide analog derivative or a nicotinamide or a nicotinamide analog metabolite, thereby expanding a population of a renewable stem cells in said sample.~~

413. (Withdrawn) A method of expanding a population of stem cells *in-vivo*, while at the same time, substantially inhibiting differentiation of the stem cells *in-vivo*, the method comprising: administering to a subject in need thereof a therapeutically effective amount of an agent, wherein said agent is selected from the group consisting of:

an agent that reduces expression and/or activity of CD38 in said stem cells,

an agent that reduces the capacity to respond to retinoic acid, retinoids and/or Vitamin D,

an agent that reduces the capacity to respond to signaling pathways involving the retinoic acid receptor, the retinoid X receptor and/or the Vitamin D receptor in said stem cells; and

an agent that is nicotinamide, a nicotinamide analog, a nicotinamide or a nicotinamide analog derivative or a nicotinamide or a nicotinamide analog metabolite.

414.(Original) The method of claim 401, wherein said stem cells are selected from the group consisting of: embryonic stem cells and adult stem cells.

415.(Cancelled)

416.(Original) The method of any of claim 401, wherein said stem cells are derived from a source selected from the group consisting of: bone marrow, peripheral blood and neonatal umbilical cord blood.

APPLICANTS: Peled et al.
SERIAL NUMBER: 10/774,843

417.(Original) The method of claim 416, wherein said stem cells are mixed with committed cells.

418.(Original) The method of claim 416, wherein said stem cells are enriched for hematopoietic CD34⁺ cells.

419.(Original) The method of claims 418, wherein said hematopoietic cells are characterized by an absence, or significantly diminished expression of cell surface antigens CD3, CD61, CD19, CD33, CD14, CD15 or CD4.

420.(Cancelled)

421. (Currently Amended) The method of claim ~~401~~20, wherein said cytokines are early acting cytokines.

422. (Original) The method of claim 421, wherein said early acting cytokines are selected from the group consisting of: stem cell factor, FLT3 ligand, interleukin-1, interleukin-2, interleukin-3, interleukin-6, interleukin-10, interleukin-12, tumor necrosis factor- α and thrombopoietin.

423.(Currently Amended) The method of claim ~~401~~20, wherein said cytokines are late acting cytokines.

424.(Original) The method of claim 423, wherein said late acting cytokines are selected from the group consisting of: granulocyte colony stimulating factor, granulocyte/macrophage colony stimulating factor, erythropoietin, FGF, EGF, NGF, VEGF, LIF, Hepatocyte growth factor and macrophage colony stimulating factor.

425. (Withdrawn)The method of claim 401, wherein providing the stem cells with *ex-vivo* culture conditions for reducing said expression and/or said activity of CD38 is by providing the cells with an agent that downregulates CD38 expression.

426. (Withdrawn) The method of claim 408, wherein said agent is an agent that downregulates CD38 expression.

427. (Withdrawn) The method of claim 425, wherein said agent that downregulates CD38 expression is selected from the group consisting of: a retinoic acid receptor antagonist, a retinoid X receptor antagonist and a Vitamin D receptor antagonist.

428. (Withdrawn) The method of claim 425, wherein said agent that downregulates CD38 expression is an antagonist for reducing a capacity of said stem cells in responding to retinoic acid, retinoid and/or Vitamin D.

429. (Withdrawn) The method of claim 425, wherein said agent that downregulates CD38 expression is a polynucleotide.

430. (Withdrawn) The method of claim 429, wherein said polynucleotide encodes an anti CD38, an anti retinoic acid receptor, an anti retinoid X receptor or an anti Vitamin D receptor intracellular antibody.

431. (Withdrawn) The method of claim 429, wherein said polynucleotide encodes an anti CD38, an anti retinoic acid receptor, an anti retinoid X receptor or an anti Vitamin D receptor antibody.

432. (Withdrawn) The method of claim 429, wherein said polynucleotide is a small interfering polynucleotide molecule directed to cause intracellular CD38, retinoic acid receptor, retinoid X receptor or Vitamin D receptor mRNA degradation.

433. (Withdrawn) The method of claim 432, wherein said small interfering polynucleotide molecule is selected from the group consisting of: an RNAi molecule, an anti-sense molecule, a ribozyme molecule and a DNzyme molecule.

434. (Withdrawn) The method of any of claim 401, wherein providing the stem cells with *ex-vivo* culture conditions for reducing said expression and/or said activity of CD38 is by providing the cells with an agent that inhibits CD38 activity.

435. (Withdrawn) The method of claim 408, wherein said agent is an agent that inhibits CD38 activity.

436. (Withdrawn) The method of claim 434, wherein said agent that inhibits CD38 activity is nicotinamide, a nicotinamide analog, a nicotinamide or a nicotinamide analog derivative or a nicotinamide or a nicotinamide analog metabolite.

437. (Withdrawn) The method of claim 436, wherein said nicotinamide analog is selected from the group consisting of: benzamide, nicotinethioamide, nicotinic acid and α -amino-3-indolepropionic acid.

438. (Withdrawn) The method of claim 436, wherein said nicotinamide analog is benzamide.

439. (Withdrawn) The method of claim 401, wherein reducing said capacity of the stem cells in responding to retinoic acid is reversible.

440. (Withdrawn) The method of claim 401, wherein reducing said capacity of the stem cells in responding to retinoic acid is by *ex-vivo* culturing the stem cells in a presence of an effective amount of at least one retinoic acid receptor antagonist, at least one retinoid X receptor antagonist and/or at least one Vitamin D receptor antagonist.

441. (Withdrawn) The method of claim 440, wherein reducing said capacity of the stem cells in responding to retinoic acid is by *ex-vivo* culturing the stem cells in a presence of an effective amount of at least one retinoic acid receptor antagonist, at least one retinoid X receptor antagonist and/or at least one Vitamin D receptor antagonist, for a time period of 0.1-50 % of an entire *ex-vivo* culturing period of the stem cells.

442. (Withdrawn) The method of claim 440, wherein said retinoic acid receptor antagonist is selected from the group consisting of: AGN 194310; AGN 193109; 3-(4-Methoxy-phenylsulfanyl)-3-methyl-butyric acid; 6-Methoxy-2,2-dimethyl-thiochroman-4-one, 2,2-Dimethyl-4-oxo-thiochroman-6-yltrifluoromethane-sulfonate; Ethyl 4-((2,2 dimethyl-4-oxo-thiochroman-6-yl)ethynyl)-benzoate; Ethyl 4-((2,2-dimethyl-4-trifluoromethanesulfonyloxy-(2H)-thiochromen-6-yl)ethynyl)-benzoate(41); Thiochromen-6-yl]-ethynyl]-benzoate(yl); (p-[(E)-2-[3',4'-Dihydro-4,4'-dimethyl-7'-(heptyloxy)-2'H-1-benzothiopyran-6'yl]propenyl]benzoic acid 1',1'-dioxide; 2E,4E,6E-[7-(3,5-Di-*t*-butyl-4-n-butoxyphenyl)-3-methyl]-octa-2,4,6-trienoic acid; 2E,4E,6E-[7-(3,5-Di-*t*-butyl-4-n-propoxyphenyl)-3-methyl]-octa-2,4,6-trienoic acid; 2E,4E,6E-[7-(3,5-Di-*t*-butyl-4-n-pentoxypheyl)-3-methyl]-octa-2,4,6-trienoic acid; 2E,4E,6E-[7-(3,5-Di-*t*-butyl-4-n-hexoxyphenyl)-3-methyl]-octa-2,4,6-trienoic acid; 2E,4E,6E-[7-(3,5-Di-*t*-butyl-4-n-heptoxyphenyl)-3-methyl]-octa-2,4,6-trienoic acid; 2E,4E,6E-[7-(3,5-Di-*t*-butyl-4-n-octoxyphenyl)-3-methyl]-octa-2,4,6-trienoic acid; (2E,4E,6E)-7-[3-*t*-butyl-5-(1-phenyl-vinyl)-phenyl]-3-methyl-octa-2,4,6-trienoic acid; 2E,4E,6E-[7-(3,5-Di-*t*-butyl-4-{[4,5-³H-_{sub}2]-*n*-pentoxy}phenyl)-3-methyl]-octa-2,4,6-trienoic acid; (2E,4E)-(1RS,2RS)-5-[2-(3,5-di-*tert*-butyl-2-ethoxy-phenyl)-cyclopropyl]-3-methyl-penta-2,4-dienoic acid ethyl ester; (2E,4E)-(1RS,2RS)-5-[2-(3,5-di-*tert*-butyl-2-ethoxy-phenyl)-cyclopropyl]-3-methyl-penta-2,4-dienoic acid; (2E,4E)-(1RS,2RS)-5-[2-(3,5-di-*tert*-butyl-2-butoxy-phenyl)-cyclopropyl]-3-methyl-penta-2,4-dienoic acid; (2E,4E,6Z)-7-[3,5-di-*tert*-butyl-2-ethoxyphenyl]3-methyl-2,4,6-octatrienoic acid; (2E,4E,6Z)-7-[3,5-di-*tert*-butyl-2-butyloxyphenyl]-3-methyl-2,4,6-octatrienoic acid; 4-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalene-carboxamido) benzoic acid; (2E,4E)-3-methyl-5-[(1S,2S)-2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-cyclopropyl]-penta-2,4-dienoic acid; p-[(E)-2-[3',4'-Dihydro-4',4'-dimethyl-7'-(heptyloxy)-2'H-1-benzothiopyran-6'-yl]propenyl]benzoic acid; 1',1'-dioxide, 4-(7,7,10,10-Tetramethyl-1-pyridin-3-ylmethyl-4,5,7,8,9,10-hexahydro-1H-naphto[2,3-*g*]indol-3-yl)-benzoic acid; (2E,4E,6Z)-7-[3,5-di-*tert*-butyl-2-methoxyphenyl]-3-methyl-2,4,6-octatrienoic acid; (2E,4E,6Z)-7-[3,5-di-*tert*-butyl-2-ethoxyphenyl]-3-methyl-2,4,6-octatrienoic acid; (2E,4E,6Z)-7-[3,5-di-*tert*-butyl-2-hexyloxyphenyl]-3-methyl-2,4,6-octatrienoic acid; (2E,4E,6Z)-7-[3,5-di-*tert*-butyl-2-octyloxyphenyl]-3-methyl-2,4,6-octatrienoic acid; and (2E,4E)-(1RS,2RS)-5-[2-(3,5-di-*tert*-butyl-2-butoxy-phenyl)-cyclopropyl]-3-methyl-penta-2,4-dienoic acid, (2E,4E,6Z)-7-(3-*n*-propoxy-5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene-2-yl)-3-methylocta-2,4,6-trienoic

acid, and 4-(5H-2,3(2,5 dimethyl-2,5-hexano)-5-n-propyldibenzo[b,e][1,4]diazepin-11-yl)benzoic acid, 4-(5H-2,3-(2,5-dimethyl-2,5-hexano)-5methyl-8-nitrodibenzo[b,e][1,4]diazepin-11-yl)benzoic acid, 4-{{4-(4-Ethylphenyl)2,2-dimethyl-(2H)-thiochromen-6-yl}ethynyl}benzoic acid, 4-[4-2methyl-1,2-dicarba-closo-dodecaboran-1-yl-phenylcarbamoyl]benzoic acid, 4-[4,5,7,8,9,10-hexahydro-7,7,10,10-tetramethyl-1-(3-pyridylmethyl)-anthra[1,2-b]pyrrol-3-yl]benzoic acid, (3-pyridylmethyl)-[5-thiaanthra[2,1-b]pyrrol-3-yl]benzoic acid, and (3-pyridylmethyl)-anthra[2m1-d]pyrazol-3-yl]benzoic acid.

443. (Withdrawn) The method of claim 440, wherein said retinoid X receptor antagonist is selected from the group consisting of:
 LGN100572, LGN100574, 1-(3-hydroxy-5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene-2-yl)ethanone, 1-(3-propoxy-5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene-2-yl)ethanone, 3-(3-propoxy-5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene-2-yl)but-2-enenitrile, 3-(3-propoxy-5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene-2-yl)but-2-enal, (2E,4E,6E)-7-3[-propoxy-5,6,7,8-tetrahydro 5,5,8,8-tetramethyl-2-naphthalene-2-yl]-3-methylocta-2,4,6-trienoic acid, 4-[3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl]carbonyl] benzoic acid, 4-[1-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)ethenyl] benzoic acid, 4-[1(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)cyclopropyl] benzoic acid, 4-[1-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)ethenyl] benzenete trazole, 2-[1-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl) ethenyl]pyridine-5-carboxylic acid, 2-[1-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)ethyl]pyridine-5-carboxylic acid, ethyl-2-[1-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)ethenyl]pyridine-5-carboxylate, 5-[1-3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)ethenyl]pyridine-2-carboxylic acid, 2-[1-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl) cyclopropyl]pyridine-5-carboxylic acid, methyl 2-[1-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)cyclopropyl]pyridine-5-carboxylate, 4-[1-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)ethenyl]-N-(4-hydroxyphenyl) benzamide, 2-[1-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl) ethenyl] pyridine-5-carboxylic acid, 2-[1-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)cyclopropyl]pyridine-5-carboxylic acid, 4-[(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)carbonyl]benzoic acid butyloxime, 4-[(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl) carbonyl]benzoic acid propyloxime, 4-[(3,5,5,8,8-pentamethyl-5,6,7,8-terrahydro-2-naphthyl)carbonyl]benzoic acid cyanoimine, 4-[(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)carbonyl]benzoic acid allyloxime, 4-

[(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)carbonyl]benzoic acid 4-(3-methylbut-2-enoic acid)oxime, and 4-[(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)carbonyl]benzoic acid 1-aminoethyloxime, (2E,4E,6Z)-7-(3-n-propoxy-5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene-2-yl)-3-methylocta-2,4,6-trienoic acid, 4-(5H-2,3(2,5 dimethyl-2,5-hexano)-5-n-propyldibenzo[b,e][1,4]diazepin-11-yl)benzoic acid, and 4-(5H-2,3-(2,5-dimethyl-2,5-hexano)-5methyl-8-nitrodibenzo[b,e][1,4]diazepin-11-yl)benzoic acid.

444. (Withdrawn) The method of claim 440, wherein said Vitamin D receptor antagonist is selected from the group consisting of: 1 alpha, 25-(OH)-D₃-26,23 lactone; 1 alpha, 25-dihydroxyvitamin D (3); the 25-carboxylic ester ZK159222; (23S)- 25-dehydro-1 alpha-OH-D (3); (23R)-25-dehydro-1 alpha-OH-D (3); 1 beta, 25 (OH)₂ D₃; 1 beta, 25(OH)₂-3-epi-D₃; (23S) 25-dehydro-1 alpha(OH) D₃-26,23-lactone; (23R) 25-dehydro-1 alpha(OH)D₃-26,23-lactone and Butyl-(5Z,7E,22E-(1S,7E,22E-(1S,3R,24R)-1,3,24-trihydroxy-26,27-cyclo-9,10-secocholesta-5,7,10(19),22-tetraene-25-carboxylate).

445. (Withdrawn) The method of claim 401, wherein reducing said capacity of the stem cells in responding to retinoids is reversible.

446. (Withdrawn) The method of claim 401, wherein reducing said capacity of the stem cells in responding to retinoids is by *ex-vivo* culturing the stem cells in a presence of an effective amount of at least one retinoic acid receptor antagonist, at least one retinoid X receptor antagonist and/or at least one Vitamin D receptor antagonist.

447. (Withdrawn) The method of claim 446, wherein reducing said capacity of the stem cells in responding to retinoids is by *ex-vivo* culturing the stem cells in a presence of an effective amount of at least one retinoic acid receptor antagonist, at least one retinoid X receptor antagonist and/or at least one Vitamin D receptor antagonist for a time period of 0.1-50 % of an entire *ex-vivo* culturing period of the stem cells.

448. (Withdrawn) The method of claim 401, wherein reducing said capacity of the stem cells in responding to Vitamin D is by *ex-vivo* culturing the stem cells in a presence of

an effective amount of at least one retinoic acid receptor antagonist, at least one retinoid X receptor antagonist and/or at least one Vitamin D receptor antagonist.

449. (Withdrawn) The method of claim 448, wherein reducing said capacity of the stem cells in responding to Vitamin D is by *ex-vivo* culturing the stem cells in a presence of an effective amount of at least one retinoic acid receptor antagonist, at least one retinoid X receptor antagonist and/or at least one Vitamin D receptor antagonist for a time period of 0.1-50 % of an entire *ex-vivo* culturing period of the stem cells.

450. (Withdrawn) The method of claim 448, wherein reducing said capacity of the stem cells in responding to signaling pathways involving the retinoic acid receptor is by *ex-vivo* culturing the stem cells in a presence of an effective amount of at least one retinoic acid receptor antagonist, at least one retinoid X receptor antagonist and/or at least one Vitamin D receptor antagonist.

451. (Withdrawn) The method of claim 450, wherein reducing said capacity of the stem cells in responding to signaling pathways involving the retinoic acid receptor is by *ex-vivo* culturing the stem cells in a presence of an effective amount of at least one retinoic acid receptor antagonist, at least one retinoid X receptor antagonist and/or at least one Vitamin D receptor antagonist for a time period of 0.1-50 % of an entire *ex-vivo* culturing period of the stem cells.

452. (Withdrawn) The method of claim 401, wherein reducing said capacity of the stem cells in responding to signaling pathways involving the retinoid X receptor is by *ex-vivo* culturing the stem cells in a presence of an effective amount of at least one retinoic acid receptor antagonist, at least one retinoid X receptor antagonist and/or at least one Vitamin D receptor antagonist for a time period of 0.1-50 % of an entire *ex-vivo* culturing period of the stem cells.

453. (Withdrawn) The method of claim 401, wherein reducing said capacity of the stem cells in responding to signaling pathways involving the Vitamin D receptor is by *ex-vivo* culturing the stem cells in a presence of an effective amount of at least one retinoic acid receptor

APPLICANTS: Peled et al.

SERIAL NUMBER: 10/774,843

antagonist, at least one retinoid X receptor antagonist and/or at least one Vitamin D receptor antagonist for a time period of 0.1-50 % of an entire ex-vivo culturing period of the stem cells.

454. (Withdrawn) The method of claim 408, wherein said cells are harvested by leukophoresis.

455. (Withdrawn) The transplantable hematopoietic cell preparation of claim 411, wherein reducing said capacity of the stem cells in responding to Vitamin D is reversible.

456. (Withdrawn) A method of preserving stem cells comprising:
harvesting said stem cells;
isolating said harvested stem cells; and
storing said isolated stem cells, wherein in at least one of said harvesting, isolating and storing steps said cells are contacted with an effective amount of an agent that substantially inhibits differentiation of said stem cells,

wherein said agent is selected from the group consisting of:

an agent that reduces expression and/or activity of CD38 of said stem cells,

an agent that reduces the capacity to respond to retinoic acid, retinoids and/or VitaminD,

an agent that reduces the capacity to respond to signaling pathways involving the retinoic acid receptor, the retinoid X receptor and/or the Vitamin D receptor in said stem cells; and

an agent that is nicotinamide, a nicotinamide analog, a nicotinamide or a nicotinamide analog derivative or a nicotinamide or a nicotinamide analog metabolite.

457. (Withdrawn) A stem cell collection/culturing bag supplemented with an effective amount of an agent that substantially inhibits differentiation of said stem cells, wherein said agent is selected from the group consisting of:

an agent that reduces expression and/or activity of CD38 of said stem cells,

an agent that reduces the capacity to respond to retinoic acid, retinoids and/or Vitamin D,

an agent that reduces the capacity to respond to signaling pathways involving the retinoic acid receptor, the retinoid X receptor and/or the Vitamin D receptor in said stem cells; and

an agent that is nicotinamide, a nicotinamide analog, a nicotinamide or a nicotinamide analog derivative or a nicotinamide or a nicotinamide analog metabolite.

458. (Withdrawn) A stem cells separation and/or washing buffer supplemented with an effective amount of an agent that substantially inhibits differentiation of said stem cells, wherein said agent is selected from the group consisting of:

- an agent that reduces expression and/or activity of CD38 of said stem cells,
- an agent that reduces the capacity to respond to retinoic acid, retinoids and/or Vitamin D,
- an agent that reduces the capacity to respond to signaling pathways involving the retinoic acid receptor, the retinoid X receptor and/or the Vitamin D receptor in said stem cells; and
- an agent that is nicotinamide, a nicotinamide analog, a nicotinamide or a nicotinamide analog derivative or a nicotinamide or a nicotinamide analog metabolite.

459. (Withdrawn) An assay for determining whether a retinoic acid receptor antagonist is an effective cell expansion agent, the assay comprising:

culturing a population of stem cells or cells of a substantially non-differentiated cell line in the presence of a test agent,

wherein said agent is selected from the group consisting of:

- an agent that reduces expression and/or activity of CD38 of said stem cells,
- an agent that reduces the capacity to respond to retinoic acid, retinoids and/or Vitamin D,
- an agent that reduces the capacity to respond to signaling pathways involving the retinoic acid receptor, the retinoid X receptor and/or the Vitamin D receptor in said stem cells; and
- an agent that is a nicotinamide analog, a nicotinamide analog derivative or a nicotinamide analog metabolite; and

monitoring expansion of said cells,

wherein increased expansion and decreased differentiation occurs in cells cultured in the presence of the test agent as compared to cells cultured in the absence of antagonist indicates said antagonist is an effective cell expansion agent.

460.(Original) An *ex-vivo* expanded population of hematopoietic stem cells, comprising: a plurality of cells characterized by 3-20 % of said cells being reselectable for CD34⁺ cells, of which at least 40 % of cells are CD34⁺ dim, wherein, in said reselectable CD34⁺ cells, a majority of cells which are Lin⁻ are also CD34⁺ dim cells.

461. (Withdrawn) A method of *ex-vivo* expanding a population of hematopoietic stem cells *ex-vivo*, the method comprising: obtaining adult or neonatal umbilical cord whole white blood cells or whole bone marrow cells sample and providing the cells in said sample with *ex-vivo* culture conditions for stem cells *ex-vivo* cell proliferation and, at the same time, for reducing a capacity of said stem cells in responding to retinoic acid, retinoids and/or Vitamin D, thereby expanding a population of a renewable stem cells in said sample.

462. (Currently Amended) A method of expanding *ex-vivo* a population of hematopoietic renewable stem cells, the method comprising:

obtaining adult or neonatal umbilical cord whole white blood cells or whole bone marrow cells sample; and

culturing said cells *ex-vivo* under conditions that result in proliferation of said cells, said conditions comprising nutrients and cytokines; and at the same time culturing said cells under one of the following conditions:

~~reducing capacity of said stem cells to respond to signaling pathways involving the retinoic acid receptor, the retinoid X receptor and/or the Vitamin D receptor;~~

~~culturing the cells in the presence of at least 0.1 mM of exogenously added nicotinamide, nicotinamide analog or nicotinamide derivativenicotinamide, a nicotinamide analog, a nicotinamide or a nicotinamide analog derivative or a nicotinamide or a nicotinamide analog metabolite;~~

~~reducing capacity of the stem cells in responding to retinoic acid, retinoids and/or Vitamin D; and~~

~~reducing capacity of the stem cells in responding to signaling pathways involving the retinoic acid receptor, retinoid X receptor and/or Vitamin D receptor;~~

thereby expanding a *ex-vivo* a population of a renewable stem cells in said sample.

APPLICANTS: Peled et al.

SERIAL NUMBER: 10/774,843

463. (Currently Amended) A method of expanding *in vivo* a population of stem cells, while at the same time, substantially inhibiting differentiation of the stem cells *in-vivo*, the method comprising: administering to a subject in need thereof a therapeutically effective amount of at least 0.1 mM of exogenously added nicotinamide, nicotinamide analog or nicotinamide derivative of an agent, wherein said agent

~~reduces capacity of said stem cells to respond to signaling pathways involving the retinoic acid receptor, the retinoid X receptor and/or the Vitamin D receptor;~~

~~reduces capacity of the stem cells to respond to retinoic acid, retinoids and/or Vitamin D; or~~

~~is nicotinamide, a nicotinamide analog, a nicotinamide or a nicotinamide analog derivative or a nicotinamide or a nicotinamide analog metabolite.~~